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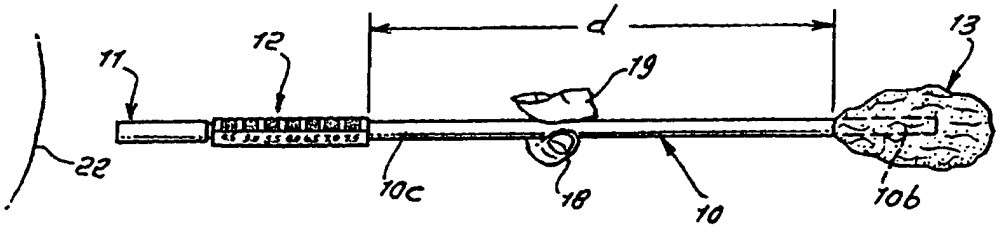

(57) Abstract

In the method of determining the need for human estrogen replacement therapy or estrogen or estradiol dose change, the steps include determining local acidity proximate a moist wall surface of the vagina or urethra as differing from a desired threshold level pH, and administering sufficient estrogen or estradiol to result in change in acidity toward such level. The determination is made by an acidity indicator (11) and pH measurement colorimeter means (12) on a carrier (10).

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ESTROGEN OR ESTRADIOL NEED DETERMINATION BY VAGINAL OR URETHRAL ACIDITY DETERMINATION

BACKGROUND OF THE INVENTION

This invention relates generally to factors involved in determining estrogen or estradiol administration to human females, and more particularly to a simple and effective method and means to effect such determination such as need for beginning estrogen replacement therapy or changes in dosage of estrogen or estradiol.

There is need for improvements in methods to determine whether or not a human female should be administered estrogen or estradiol or needs a higher or lower dose of estrogen or estradiol. The present invention addresses that need.

SUMMARY OF THE INVENTION

It has been discovered that the acidity (pH) or pH(acidity) level of a moist wall surface of the vagina or urethra can be employed in estrogen or estradiol need determination. In accordance with the invention, the method of determining need for estrogen or estradiol increase or decrease includes the steps:

a) determining local acidity proximate a moist wall surface of the vagina, or urethra, as differing from desired threshold level, and in the substantial absence of bacterial vaginosis, or other contaminants such as medications, blood, semen,

b) and administering sufficient estrogen or estradiol to result in change in acidity toward such level or a pH of about 4.5 without menopausal signs or symptoms.

Typically, administering of sufficient estrogen or estradiol may be

effected on a periodic regular basis, as for example increased or decreased dosage (for example orally) on a daily basis, and in increasing amounts, and said determination of local acidity is repeated, whereby said local acidity is ultimately determined to have reached said desired level.

Yet another object is the carrying out of such determination of local acidity as by employing an acidity indicator, for contacting the wall surface of the vagina or urethra. Such an indicator may desirably include one of the following:

i) NITRAZINE ® paper

ii) phenaphthazine on a carrier

iii) a material or materials exhibiting different colorations or other indicators as a function of pH level.

A strip of material may be used to carry the indicator, and such a strip may be employed in contacting the vaginal or urethral wall. One method of use is to provide the strip of material on an applicator, an example being a carrier stick which is easily manipulable.

A further object is to provide a pH level indicator comprising a material or materials exhibiting colorations corresponding to pH levels of moisture of the wall surface of the vagina, or urethra, said colorations being different for different pH levels. The desired threshold level of acidity is approximately 4.2 - 4.5.

Yet another object is to provide a method that includes the steps:

a) providing an acidity sensing means on a carrier,

b) providing a protective porous layer adjacent said sensing means,

c) manipulating the carrier proximate vaginal moisture, and including allowing vaginal and/or urethral moisture to penetrate said porous layer for contact with said sensing means,

d) and detecting a vaginal and/or urethral moisture produced change in said sensing means for determining need for beginning estrogen

replacement therapy or a change in estrogen or estradiol dose to be administered to a human female.

An additional object is to measure vaginal or urethral pH for screening purposes, a vaginal or urethral pH level of 4.5 being consistent with a physiologic serum estradiol and the absence of bacterial vaginosis. An elevated vaginal pH in the 5.0-6.5 range suggests a diagnosis of either bacterial vaginosis or decreased serum estradiol. In patients with an elevated pH, vaginal culture should establish the diagnosis. In the absence of vaginosis, a vaginal pH of 6.5-7.5 is strongly suggestive of a low serum estradiol or menopause. Titration of estradiol level by vaginal or urethral pH during estrogen replacement therapy is then carried out.

These and other objects and advantages of the invention, as well as the details of an illustrative embodiment, will be more fully understood from the following specification and drawings, in which:

DRAWING DESCRIPTION

Fig. 1 is a side elevational view of stick apparatus incorporating the invention;

Fig. 2 is an enlarged side view of one end portion of the Fig. 1 stick apparatus;

Fig. 3 is an enlarged section taken on lines 3-3 of Fig. 2;

Fig. 4 is an enlarged end view taken on lines 4-4 of Fig. 2;

Fig. 5 is an elevation, partly in section, showing a modification;

Fig. 6 is a side elevation of the Fig. 5 modification;

Fig. 7 is an end view taken on lines 7-7 of Fig. 6;

Fig. 8 is an elevation showing a further modification;

Fig. 9 is an elevation showing yet another modification;

Fig. 10 is a view like Fig. 2, showing a protective porous layer applied over a pH indicator strip;

Fig. 11 is a view like Fig. 10, but showing the protective layer also applied over the color comparison measurement means;

Fig. 12 is a view like Fig. 8, showing a protective porous layer applied over a pH indication strip;

Fig. 12a is a view like Fig. 12, but showing the protective porous layer extending over the color comparison measurement means;

Fig. 13 is a perspective view showing pH indicator manipulation manually;

Fig. 14 is a plan view of the top side of a modified stick apparatus;

Fig. 15 is a plan view of the bottom side of the Fig. 14 stick apparatus;

Fig. 16 is an edge view taken on lines 16-16 of Fig. 14;

Fig. 17 is an end view taken on lines 17-17 of Fig. 16;

Fig. 18 is a plan view of modified apparatus; and

Fig. 19 is an enlarged section taken on lines 19-19 of Fig. 18.

DETAILED DESCRIPTION

As referred to, the method of the invention concerns determining need for estrogen replacement therapy or estrogen or estradiol dose change, through vaginal wall moisture pH determination or urethral wall moisture pH determination. Typical steps include:

a) determining local acidity proximate a moist wall surface of the vagina or urethra, as differing from desired threshold level, as in the substantial absence of bacterial vaginosis, or other contaminants such as medication, blood, semen,

b) and administering sufficient estrogen or estradiol to result in change in said acidity toward said level.

A more complete method includes:

a) first determining local acidity proximate a moist wall surface of the vagina, said determining employed as an indicator of the presence or absence of bacterial vaginosis,

b) and, after a vaginosis condition has been treated and eliminated, then again determining local acidity proximate a moist wall surface of the vagina, as differing from desired threshold level,

c) and administering sufficient estrogen or estradiol to result in change in said acidity toward said threshold level.

A pH indicator **100**, as seen in Fig. 13 may be employed, and that indicator may be located on a carrier strip **101**, which is easily manipulable into contact with the vaginal or urethral wall, shown at **102**, the user's finger shown at **103** to urge the tissue strip toward the wall surface. Such an indicator may take the form of one of the following, although other indicators are usable.

i) NITRAZINE® paper

ii) phenaphthazine on a carrier

iii) a material or materials exhibiting different colorations or other indicators as a function of pH level.

The indicator may desirably exhibit different colorations or changes corresponding to different pH levels, of moisture at the vaginal or urethral wall, and from which the observed coloration or changes may be used to indicate need for greater or lesser estrogen or estradiol dosage, as on a daily or other periodic basis. In the case of NITRAZINE® paper (phenaphtazine), the correlation of pH to color is as follows:

pH	Color

4.5	golden yellow
5.0	beige
5.5	light olive
6.0	dark olive
6.5	olive blue
7.0	purple blue
7.5	dark blue

In a typical example, if the user detected or determined an indicator color of dark olive, it would be determined that an estrogen or estradiol increase above the existing daily level of use would be recommended, in order to diminish pH level to 4.2 to 4.5 within one to two weeks, for example. Testing would be performed on a once a week basis. Thus, if the user had been taking 1 mg. of estrogen or estradiol per day, for example orally, she would be recommended to increase that level to 1.5 mg. per day, the objective being to reduce the pH level to about 4.5 within about 10-21 days. If the tested color were not golden yellow (4.5 pH) after 7-8 days, the dosage might be increased to 2.0 mg. level, per day, until a golden yellow color of the test strip was achieved. Thus, pH determination is indicative of need for change in estrogen or estradiol dosage (up or down).

The indicator may alternatively be employed on a manipulable apparatus, as for example a carrier stick. In Figs. 1-4, an elongated, narrow carrier stick **10** may consist of wood, plastic, or other material. Provided on the carrier stick are:

- a pH indication means, as generally shown at **11**, at one end portion **10a** of the stick; and
- a color comparison pH measurement means, as generally indicated at **12**, spaced from stick end portion **10a**, but close to **11**;

As shown, the first means **11** may comprise a pH indication strip, such as a NITRAZINE® (Phenaphthazine) strip, wound about the stick end portion **10a** and adhered to same as by an adhesive. NITRAZINE® (Phenaphthazine) strips are products of Bristol-Myers Squibb. The color comparison pH measurement means **12** may comprise a thin paper strip adhered to the stick surface to extend lengthwise of the stick from the edge or end **11a** of the first means **11**. The second means is shown to have color gradations in a series sequence, as in colored bands **12a**, positioned lengthwise of or along the stick. In addition, the paper strip **12** may include pH numerical indicators **12b** along side the color gradation bands, to enable:

- visual color comparison of the pH indication means **11** (immediately after its exposure to vaginal or urethral fluid or moisture) with the bands **12a**, for visual selection of that band most close in color to the color of the indication means **11**;
- and immediate visual readout of the pH number adjacent the selected band.

Such readout of pH is then compared with the desired level of about 4.2 - 4.5 to enable determination of a recommended dosage of estrogen or estradiol, as on a daily basis.

The stick projects freely at **10c** away from the first and second means **11** and **12** for manual manipulation (see the grasping finger and thumb **18** and **19**), to first obtain pH indication of vaginal or urethral wall moisture at one end of the stick, and to enable visual interpretation of that indication by color comparison with the second means, without manual release of the stick. The stick is then disposable, or may be disposed of.

Lengthwise spacing "**d**" between **12** and stick end **10d** is such as to enable free manual manipulation of the stick; and such spacing is typically

between 3 and 5 inches, enabling ready finger grasping of the stick and manipulation thereof. In a specific example, "d" is about 4 inches, and the stick diameter or width is about 3/16 to 3/8 inch.

The method of measuring pH of vaginal moisture includes the steps:

a) providing a pH indicator on a carrier stick,

b) manipulating the stick to obtain pH indication of vaginal or urethral wall moisture at said indicator,

c) visually interpreting that indication to determine need for a change in estrogen or estradiol dosage,

d) and disposing of the stick,

The overall sizes of **11**, **12** and **13** are such as to enable ready insertion into the vagina, or urethra, or application to a surface of the vagina or urethra, via stick manipulation at zone **10c**.

Referring now to the modification shown in Figs. 5-7, a smooth surfaced protective tip **20** is provided to face endwise at the end **10aa** of the stick end portion **10a**. As shown, the tip **20** is endwise convex, as for example bulbous, to provide for or enable comfortable insertion of the stick end portion **10a** into the vagina or urethra, for pH measurement. The tip **20** may typically be formed integrally with a sleeve **20a** assembled over and closely fitting the measurement strip **11**, and may be suitably adhered thereto, locally, as at **21**. A suitable bonding agent is epoxy. The remainder of the strip **11** is therefore available for pH indication. Alternatively, the sleeve may be attached, as by heat shrinking, or by wedge fit.

A fluid access opening is provided through the wall of the sleeve, whereby vaginal moisture or fluid may access the strip **11** via that opening. See for example elongated slot **22** in the sleeve wall **20aa**. The sleeve and tip may consist of transparent, molded, plastic material, to facilitate viewing of a change of color of the strip **11**.

In Fig. 8, the sleeve **20a** is shortened and attached at sleeve end **20a'** into flush, or near flush, relation with the surface of the strip, at a locus on stick end portion **10a**. This leaves the remaining length **11f** of the strip openly exposed for moisture contact.

In Fig. 9, the sleeve **20a''** is also shortened and attached to the stick end portion **10a**, and in endwise alignment with the strip **11**. This also leaves the remaining length **11f'** of the strip openly exposed for moisture contact.

Referring now to the modification seen in Fig. 10, the elements the same as in Fig. 2 are given the same numerals. In addition a protective layer **40** in the form of a thin porous barrier, is applied adjacent the outer side of strip **11** so as to cover the latter (i.e. extend thereabout) and to be carried by the stick. Layer **40** allows vaginal moisture to penetrate through it and to contact the pH indicator strip **11**, as during a test. Following the test, the strip **11** may be observed as described above, and for this purpose the layer **40** may be at least partly removed from adjacency to the strip, as by complete manual removal. Opposite end portions **40a** and **40b** of layer **40** may be initially attached as by light bonding or sticking to the ends of the strip **11**, or to the stick, allowing pull-away removal of the layer at the end of the test. Such bonding agents are known, as on 3M Micropore Tape. Layer **40** acts as a barrier, during a test, to block direct contact of vaginal tissue or urethral tissue with strip **11**, preventing any possible irritation of such tissue.

In Fig. 11, the elongated layer **45** is like layer **40**, but also extends over and about the color comparison measurement means **12**, and is adhered, as described above, to the elements **11** and **12**, as at **45a** and **45b** to completely cover **11** and **12** as during a test, while allowing pull-away of the layer **45** for visual observation of **11** and **12** after the test. Either one or both of **11** and **12** may be considered as a pH detecting means.

Fig. 12 is like Fig. 8, but layer **50** corresponding to layer **40** has its

end **50a** adhered to and about the sleeve **20a'**, while end portion **50b** is adhered to the right end of strip **11**, as shown. Note smooth surfaced blunt knob **20**, as referred to above.

Fig. 12a is like Fig. 12, except that the layer **60**, corresponding to **50**, is elongated to cover the color comparison measurement means **12**, and to adhere at **60b** to the rightward end of **12**.

In Figs. 10-12a, the porous barriers, as at **40**, **45**, **50** and **60** may consist of one or more barrier tissue layers, as for example are used in incontinence pads. One example is the outer layer of the Kimberly Clark product NEW DEPEND. Another usable barrier is the 3M product known as MICROPORE tape. One side of such tape is "tacky", i.e. weakly adhesive, so that it will adhere along the tape length to the elements **11** and/or **12** referred to. Barriers **45** and **50** as referred to may comprise such tape material.

In Figs. 14-17, a modified elongated, narrow carrier stick **200** may consist of wood, plastic or other carrier material. A pH indication strip **201** such as phenaphthazine paper is adhered to one substantially flat side **200a** of the stick **200**, and near one end **200b**, as by an adhesive. The strip **201** is elongated, and spaced from opposite edges **200c** and **200d** of the stick, as well as from end **200b**. Typically, rectangular strip width is about .25 inches, and its length is about 1.5 inches. The stick width is about .375 inches, its length is about 5 inches and its thickness is about .125 inches.

The stick edges **200c** and **200d** are convexly curved or rounded as at **210** and **211** in Fig. 17. Also, the stick opposite ends **200f** and **200g** are convexly curved or rounded as at **212** and **213**.

The handle portion **200e** of the stick is desirably textured, as by provision of dimples **215** on side **200a** of the stick. The length of such texturing may be about 1.5 inches, from end **200b**. Such texturing aids finger and thumb gripping of the handle portion for accurate stick manipulation to position strip **201**

adjacent the vaginal wall. Aiding of manipulation of the paper strip is enhanced by locating the texturing and paper strip at the same side of the stick. Note that the stick preferably has smooth top surface extent at **220** between **215** and **201**, and also a smooth bottom surface at **221**.

Figs. 18 and 19 show yet another and preferred kit in which an indicator strip or tip **228** (corresponding to strip or tip **111**) is carried at the left end of elongated stick **229**. A swab **233** is carried at the right end of the stick. An encapsulating, thin, flexible, transparent receptacle **230** protectively contains the elongated stick, tip **228** and swab **233**, and may be torn open to retrieve the stick. The receptacle may consist of thin walled plastic sheets **230a** and **230b** bonded together along sheet edge portions indicated at **250, 251, 252** and **253**, whereby the receptacle is sealed.

A thin, elongated paper insert sheet **260** is also received in the receptacle, to overlie most of stick **200**, whereby use instruction and identification data may be printed on the sheet **260** and presented upwardly or outwardly for viewing through the transparent upper sheet **230a**. Sheet **260** defines a narrow window or cut-out at **261**, which is elongated along a mid-portion **262** of sheet **260**, as shown.

Color comparison elements such as bands are carried by the insert sheet **260**, as in two rows shown at **228a** and **228b**, at opposite sides of the window. Preferably, the longitudinally spaced bands extend to laterally spaced edges of the window, for ease of color comparison of the indicator (after its exposure to moisture as described above) with the different bands. Sheet **260** may be eliminated, and the bands printed or affixed on the receptacle top sheet, to define the window.

Longitudinally spaced bands have different colors, while laterally oppositely spaced bands have the same color. Note their pH numerical labeling, at 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, and 7.5, along the window length.

In use, the right end of the receptacle is opened, and the carrier stick **229** is withdrawn, for use. Thereafter, the indicator tip **228**, which may be cylindrical, after its exposure to moisture, is re-inserted into the elongated receptacle **230**, under the insert sheet **260**, to bring tip **228** under the window **261**. Tip **228** preferably has a width or diameter greater than the window width, so that it adjacently registers with the successive bands in the two rows as the tip moves longitudinally. This facilitates ease of color comparison use. The tip and stick remain in the receptacle, for ease of disposal.

In addition to provision and manipulation of a first carrier stick as referred to, with respect to vaginal or urethral moisture samples, the method may also include providing an elongated second carrier having a second pH detector on that carrier at an end position thereof, and manipulating the second carrier to effect exposure of the second detector to vaginal or urethral moisture, thereby to cause the second detector to exhibit a color change, and comparing the color changes exhibited by the first and second detectors. If color changes exhibited (due to both vaginal and urethral moisture contact with the detector) are the same, a validity check is thereby provided.

Accordingly, the method of determining validity of pH of body moisture or fluid may include:

a) determining pH of vaginal moisture or fluid, by employment of a first indicator,

b) also determining pH of urethral moisture or fluid, by employment of a second indicator.

The two indicators may then be compared, as for example by comparison of color changes produced on or by the indicators. The indicators themselves would be identical as to color change capability.

EXAMPLES

OBJECTIVES:

To confirm the elevation of vaginal pH expected in patients with bacterial vaginosis and to examine the relationship of serum FSH and estradiol levels to vaginal pH in normal patients without vaginosis.

STUDY DESIGN:

2,038 patients in a solo private practice underwent measurement of vaginal pH during routine pelvic examinations. 201 of these patients were chosen at random for this study. Measurements were made of serum levels of FSH and estradiol. Vaginal cultures were taken from 83 patients. Specimens were sent to a single commercial laboratory. Vaginal pH was determined by phenaphthazine (NITRAZINE®) pH paper. Vaginal pH was correlated with serum FSH, estradiol levels, and vaginal cultures using statistical analysis.

RESULTS:

Vaginal pH was elevated in patients with documented vaginosis. Serum estradiol levels showed an inverse and serum FSH levels showed a direct statistical correlation with vaginal pH.

MATERIALS AND METHODS:

Between May 1995 and May 1996, 2,038 patients in a private gynecologic practice were tested for vaginal pH. None of the patients were pregnant.

A total of 83 patients had vaginal cultures to study the effect of vaginosis on vaginal pH.

Two hundred one patients were tested for vaginal pH, serum FSH and serum estradiol. Of these 201 patients, 100 were on Estrogen Replacement Therapy and 8 were on oral contraceptives. Ninety-three patients were on no

hormonal treatment. No patients tested were using vaginal medication.

Eighteen patients were tested for vaginal pH, serum FSH and serum estradiol on two separate occasions. Nine of these patients were tested before and after the use of estrogen. Nine patients were tested after a change in estrogen dose. In all nine cases, the estrogen does was increased. This separate study was done to observe the change in vaginal pH, serum FSH and serum estradiol in response to a change in estrogen therapy.

Phenaphthazine (NITRAZINE®) pH indicator paper was used for vaginal pH testing (NITRAZINE® pH indicator paper pH 4.5 to 7.5 range, distributed by APOTHECON®, a Bristol-Myers Squibb Company, Princeton, New Jersey). This pH paper has been used for vaginal pH testing since 1938. The extended range of pH 4.5 to 7.5 proved to be easier to read and more comprehensive for vaginosis and vaginal estrogen level. Other pH testing papers were tried. (Hydrion® pH papers, Micro Essential Laboratory, 4224 Avenue H, Brooklyn, New York 11210 (718) 338-3618). (ColorpHast® pH test strips, EM Science, 480 Democrat Road, Gibbstown, New Jersey 08027 (800) 222-0342).

The pH paper was applied directly to the lateral vaginal wall at the outer third of the vagina. Care was taken to avoid cervical mucous (pH 7.0), blood (ph 7.4), or other substances (such as semen pH 7.0-8.0) and lubricating jelly known to affect vaginal pH. All samples were interpreted in incandescent light for accuracy.

All vaginal cultures were collected using the Star Swab, Starplex Transport System and were sent to Unilab Corporation, Tarzana, California. Venopuncture for blood samples was obtained within one hour of the vaginal pH test. Serum FSH was run on the Dade/Baxter, Inc. Stratus II automated instrument and reported as miU/mL. Female normal ranges are: Follicular Phase:

3.6-16.0 miU/ml, Mid Cycle Peak: 8.1-28.9 miU/ml, Luteal Phase: 1.8-11.7

miU/mL and Post Menopausal:
22.9-167.0 miU/mL. Serum estradiol was determined by radio immune assay, using Diagnostics Products Corporation's Coat A Count and reported as pg/mL. The normal range is 10-375. All tests were done at Huntington Memorial Hospital laboratory, Pasadena, California. Statistical analysis was performed by using the computer program "Statistical Package for Social Sciences" (SPSS).

Relationships between vaginal pH, serum estradiol and FSH levels were evaluated using Spearmans's Correlation Coefficients. Treated and untreated groups were compared for these variables using t-tests and ANOVA with Duncan Multiple Comparisons. Paired t-tests were used to compare the difference in means due to initiation or change of estrogen therapy.

RESULTS:

Of 84 patients who had vaginal cultures, 27 grew normal flora, 14 yeast, 15 Beta-hemolytic-streptococcus, 14 gardnerella, and 13 mixed pathogens. The mean pH of three subgroups with bacterial vaginosis is significantly higher than that obtained in patients with either normal flora or yeast infection (One way ANOVA, $p<0.05$). There was no significant difference in the vaginal pH among the three subgroups with bacterial vaginosis, and there was no significant difference between the pH in patients with yeast infection and those with normal flora.

In the overall group of 201 women tested for vaginal pH, estradiol and FSH, vaginal pH correlated positively with serum FSH levels and negatively with serum estradiol using Spearman's correlation coefficients.

When the group of 201 women was divided into those on estradiol therapy and those on no treatment, significant differences were found between mean vaginal pH, serum estradiol levels, and serum FSH levels. These differences were significant despite the inclusion of some apparently normally

cycling women in the untreated group. There was no significant difference in the mean age of the patients between the two groups.

The characteristics of 18 women studied both before and after initiation ($n=9$) or change ($n=9$) of estrogen replacement therapy showed that serum estradiol levels increased and FSH levels decreased significantly after initiation or changes of dose of ERT ($p<0.003$ and $p<0.001$ respectively, using paired t-testing). There was a significant decrease in vaginal pH from 6.1 ± 0.7 to 4.6 ± 0.3 ($p<0.001$) in the group who went from no treatment to estrogen replacement. Mean vaginal pH also decreased, although to a lesser degree of significance, in the women who went from lower dose to higher dose ERT ($p=0.05$).

The data obtained support the well documented body of literature indicating that vaginosis results in an elevated vaginal pH (5.0-6.5). For this reason alone, vaginal pH should become a routine test during most speculum examinations. Women should be encouraged to do vaginal pH testing to alert both pregnant and non-pregnant women to the possibility of sub-clinical vaginosis and to seek medical advice for proper diagnosis and treatment. The combination of pH testing, vaginal culture, and treatment as indicated, have shown a decrease in premature rupture of membranes and premature delivery.

The editorial comments of Watson A. Bowes, Jr. in the May 1996 issue of Obstetrical and Gynecological Survey are pertinent.

Statistically significant is the fact that the vaginal pH level, in the absence of vaginosis, is a reasonable marker for most patient's estradiol status. In addition, an elevated vaginal pH level in a well estrogenized patient is a reasonable marker for vaginosis. In this regard, detected pH correlates positively (directly) with FSH; and pH correlates negatively (inversely) with estradiol intake.

In consideration of all that as been said, vaginal and/or urethral

testing for pH level appears to be that hoped for, reliable, "low-tech" tool. It certainly complies with the mandate for cost-effective, improved health care.

In the above, estrogen or estradiol can be administered orally, intermuscularly, or vaginally.

CLAIMS

1. In the method of determining need for human estrogen or estradiol level change, the steps that include:

a) determining local acidity proximate a moist wall surface of the vagina, as differing from desired threshold level,

b) and administering sufficient estrogen or estradiol to result in change in said acidity toward said level,

c) said administering of estrogen or estradiol being effected on a periodic basis.

2. The method of claim 1 wherein said administering of sufficient estrogen or estradiol is effected on a periodic basis, and in increasing amounts, and said determination of local acidity is repeated, whereby said local acidity is ultimately determined to have reached said desired level.

3. The method of claim 1 wherein said determining of local acidity includes employing an acidity indicator, and effecting contact of said indicator with said wall surface of the vagina or urethra.

4. The method of claim 3, wherein said indicator includes one of the following:

i) NITRAZINE® paper

ii) phenaphthazine on a carrier

iii) a material or materials exhibiting different colorations as a function of pH level.

5. The method of claim 1 wherein said threshold level is approximately 4.2

pH.

6. The method of claim 3 including providing a strip of material carrying said acidity indicator, and said determining of local acidity includes first contacting said strip with the wall surface of the vagina, or urethra, and then observing said indicator on the strip.

7. The method of claim 6 wherein said indicator comprises a material or materials exhibiting colorations or other indications corresponding to pH levels of moisture of the wall surface of the vagina, or urethra, said colorations being different for different pH levels.

8. The method of claim 3 including providing an elongated applicator on which said indicator is mounted, and manipulating said applicator to bring said indicator into said contact with the vaginal or urethral wall surface.

9. The method of claim 8 including providing said indicator in the form of a strip of material or materials mounted on an end portion of the applicator.

10. The method of claim 6 including manually manipulating said strip of material into contact with the wall surface of the vagina, or urethra.

11. In the method of determining need for human estrogen or estradiol change, the steps that include:

a) first determining local acidity proximate a moist wall surface of the vagina, or urethra, said determining employed as an indicator of the presence or absence of bacterial vaginosis,

b) and, after a vaginosis condition has been treated and eliminated,

then again determining local acidity proximate a moist wall surface of the vagina or urethra, as differing from desired threshold level,

c) and administering sufficient estrogen or estradiol to result in change in said acidity toward said threshold level.

12. The method of claim 11 wherein said administering of estrogen or estradiol is effected periodically and orally.

13. The method of claim 11 wherein said administering of sufficient estrogen or estradiol is effected on a periodic basis, and in increasing or decreasing amounts, and said determination of local acidity is repeated, whereby said local acidity is ultimately determined to have reached said desired level.

14. The method of claim 11 wherein said determining of local acidity includes employing an acidity indicator, and effecting contact of said indicator with said wall surface of the vagina or urethra.

15. In the method of determining need for human estradiol level change, the steps that include:

a) determining local acidity proximate a moist wall surface of the vagina, as differing from desired threshold level,

b) and administering sufficient estrogen or estradiol to result in change in said acidity toward said level, said administering of estrogen or estradiol being effected on a periodic basis,

c) said determining of local acidity including

i) employing an acidity indicator, and effecting contact of said indicator with said wall surface of the vagina,

ii) and providing an elongated applicator on which said indicator

is mounted, and manipulating said applicator to bring said indicator into said contact with the vaginal wall surface,

d) said determining including providing an elongated pH measurement colorimeter mean, and mounting said means to extend with elongation in the direction of elongation of said applicator.

16. In the method of employing detected pH of vaginal or urethral moisture in estrogen therapy, the steps that include:

a) providing an acidity sensing means on a carrier,

b) providing a protective porous layer adjacent said sensing means,

c) manipulating the carrier proximate vaginal or urethral moisture, and including allowing vaginal or urethral moisture to penetrate said porous layer for contact with said sensing means,

d) and detecting a vaginal or urethral moisture produced change in said sensing means, for determining need for a change in estrogen or estradiol dosage.

17. The method for measuring pH of vaginal or urethral moisture for determining need for a change in estrogen or estradiol dosage, that includes providing an elongated carrier, providing a pH indicating detector on the carrier, providing color comparison measurement means, providing a longitudinally elongated receptacle for said carrier and detector, said color comparison measurement means provided in association with the receptacle, there being a longitudinal window along which said color comparison measurement means is displayed in the form of bands, and manipulating said detector within the receptacle and along the window for visual color comparison with said bands, after exposure of said detector to vaginal or urethral moisture.

18. The method of claim 17 wherein said bands are provided in two longitudinal rows, at laterally opposite sides of said window.

19. The method of claim 18 wherein said detector is provided to have a lateral dimension greater than width of the window, and said bands are provided to extend proximate the window, and said detector is displaced longitudinally in proximate adjacency to the bands at opposite sides of the window.

20. An apparatus for measuring pH of vaginal or urethral moisture for determination of need for change in estrogen or estradiol dosage, comprising in combination:

a) an elongated carrier,

b) pH indicating means on the carrier, at one end portion thereof, and sized for application to a zone adjacent the wall of thc vagina or urethra.

21. An apparatus for measuring pH of vaginal or urethral moisture for determination of need for a change in estrogen or estradiol dosage, comprising in combination:

a) an elongated carrier,

b) pH indicating first means in the form of a strip on the carrier, at one end portion thereof,

c) color comparison pH measurement second means on the carrier, spaced from said one end portion thereof,

d) the carrier projecting freely from said first and second means for manual manipulation to first obtain pH indication of vaginal or urethral moisture at said one end of the carrier, and to enable

interpretation of that indication by color comparison with said second means,

e) the carrier then being disposable to dispose of both said first and second means in one disposal step,

f) there being a protective porous layer extending adjacent at least one of the following:

x_1) said strip

x_2) said color comparison measurement means.

22. The apparatus of claim 21 including a smooth surfaced protective tip facing endwise at said one end of the carrier.

23. The apparatus of claim 21 wherein said second means has color gradations in a series sequence on the carrier.

24. The apparatus of claim 23 wherein there are pH numerical indications on the carrier, in close association with said color gradations.

25. The apparatus of claim 22 including a protective plastic sleeve extending about a portion of said carrier in endwise alignment with said strip, said sleeve carrying said tip.

26. The combination that comprises a package including an elongated carrier, a pH indicating detector on the carrier, color comparison measurement elements, said package also including a longitudinally elongated receptacle for said detector, said color comparison elements positioned in association with the receptacle, there being a longitudinal window along which said color comparison elements are displayed, whereby the detector may be

manipulated within the receptacle and along the window for visual color comparison with said elements, after exposure of the detector to vaginal or urethral moisture.

27. The combination of claim 26 wherein said elements extend in two longitudinal rows, at laterally opposite sides of said window.

28. The combination of claim 27 wherein said detector has lateral dimension matching or exceeding the width of the window and said elements extend into proximity to the window, whereby the detector may be displaced longitudinally in proximate adjacency to successive of said elements at opposite sides of the window.

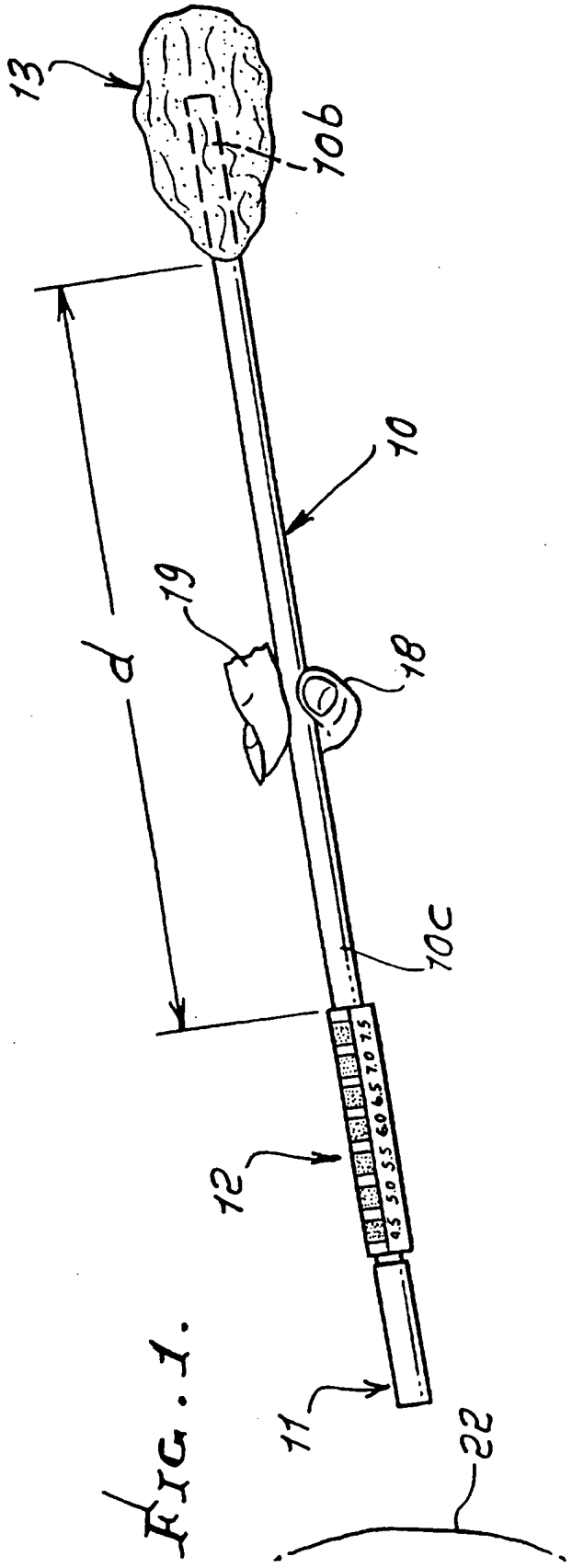
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FIG. 1.

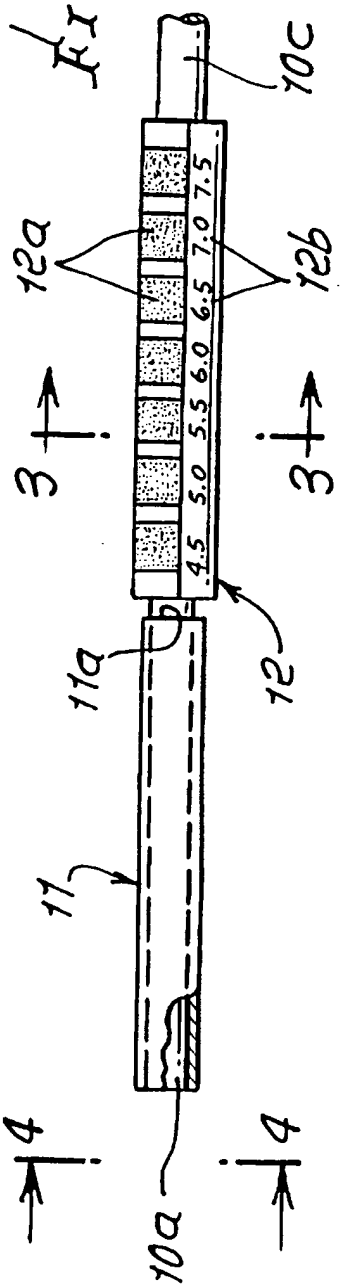
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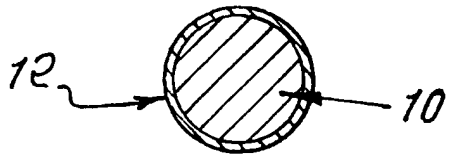
FIG. 2.

FIG. 3.



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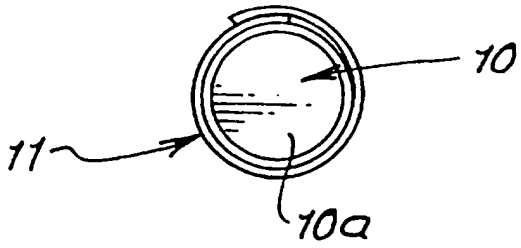
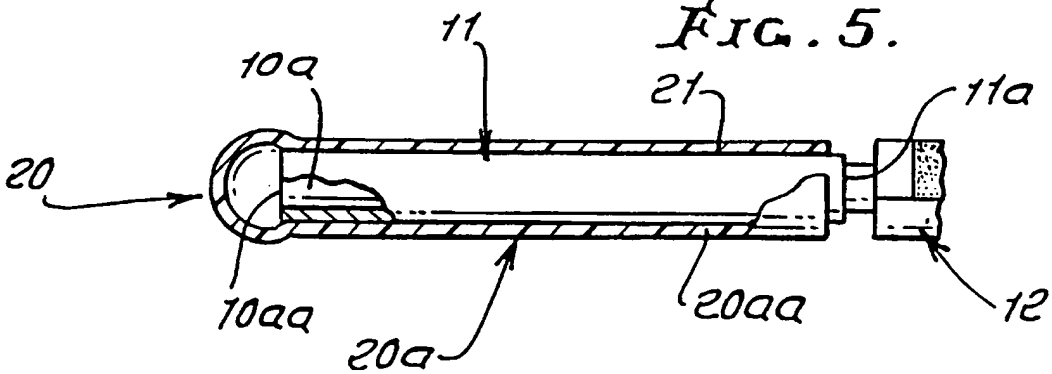


FIG. 5.



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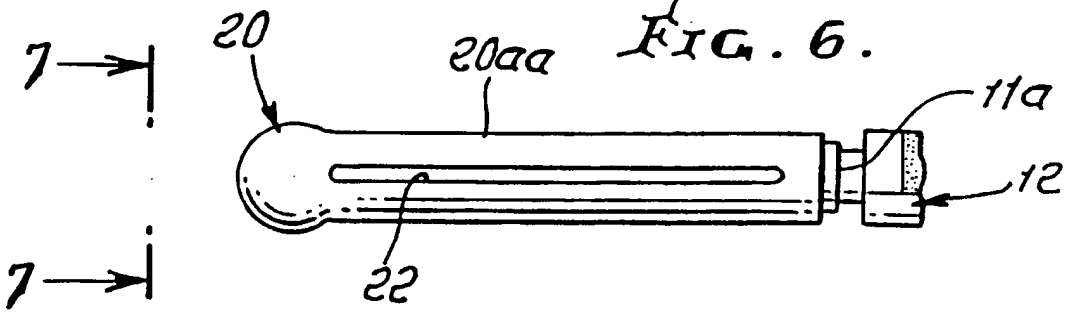

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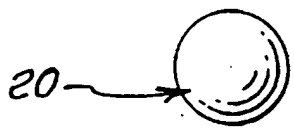

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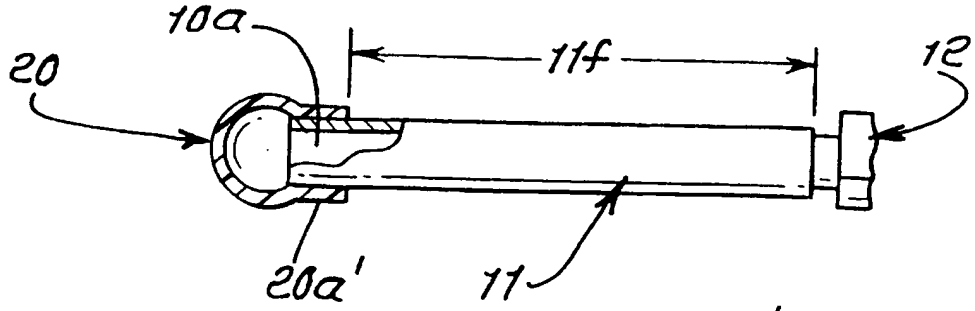
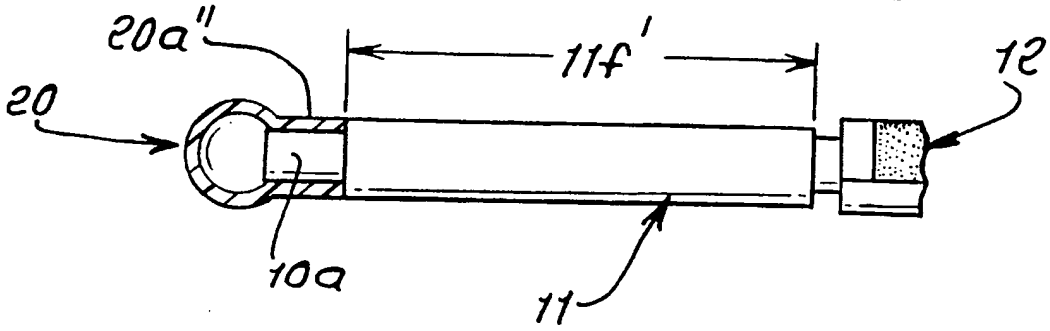


FIG. 9.



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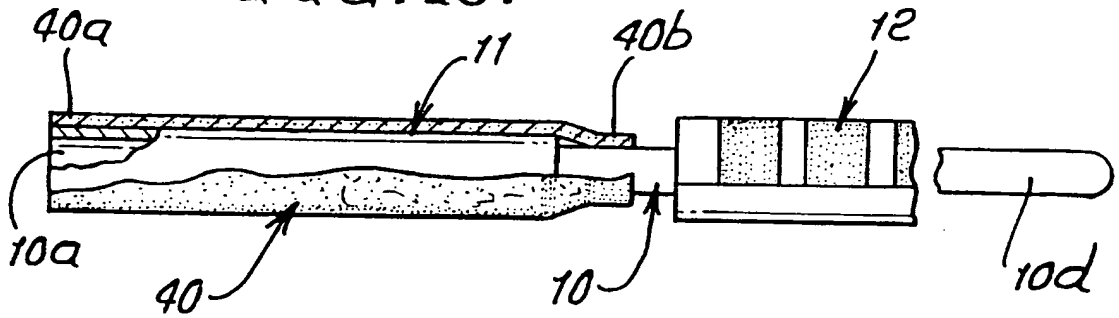
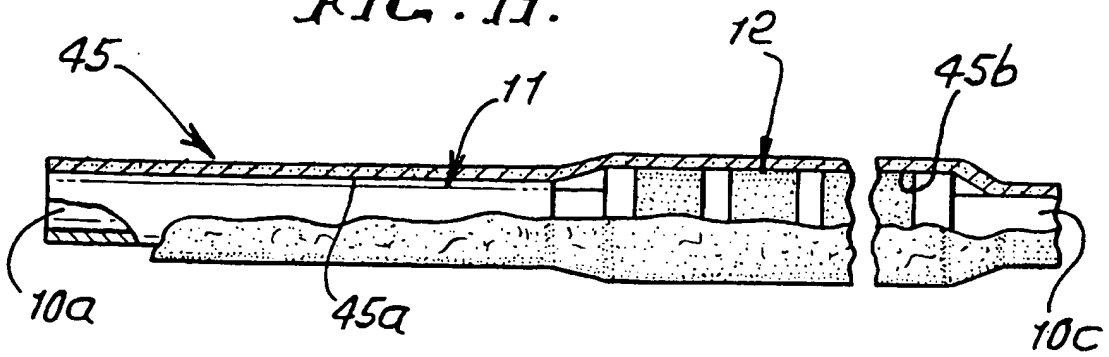


FIG. 11.



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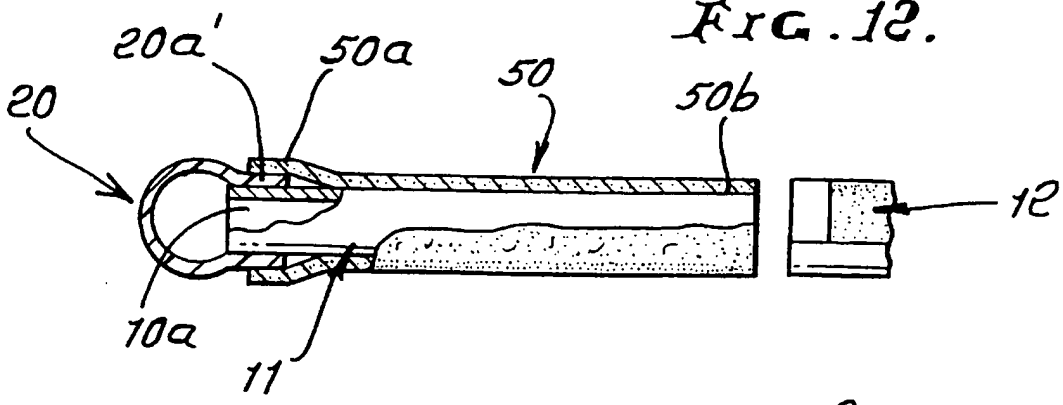
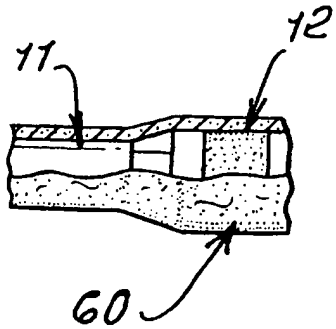


FIG. 12a.



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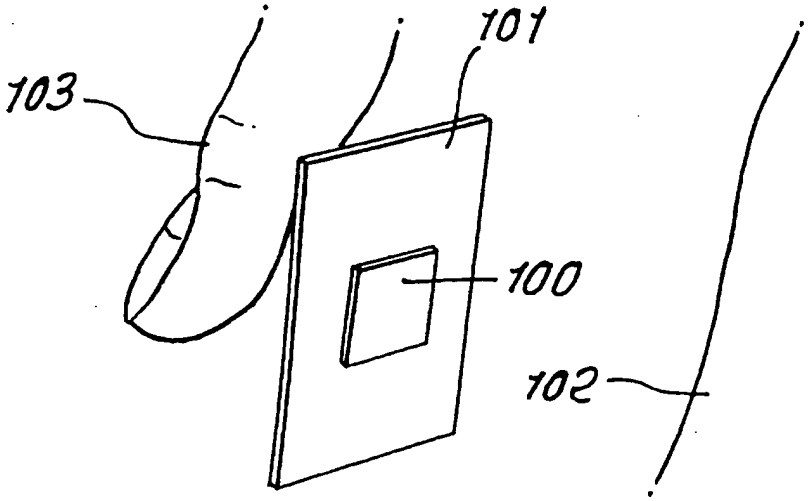

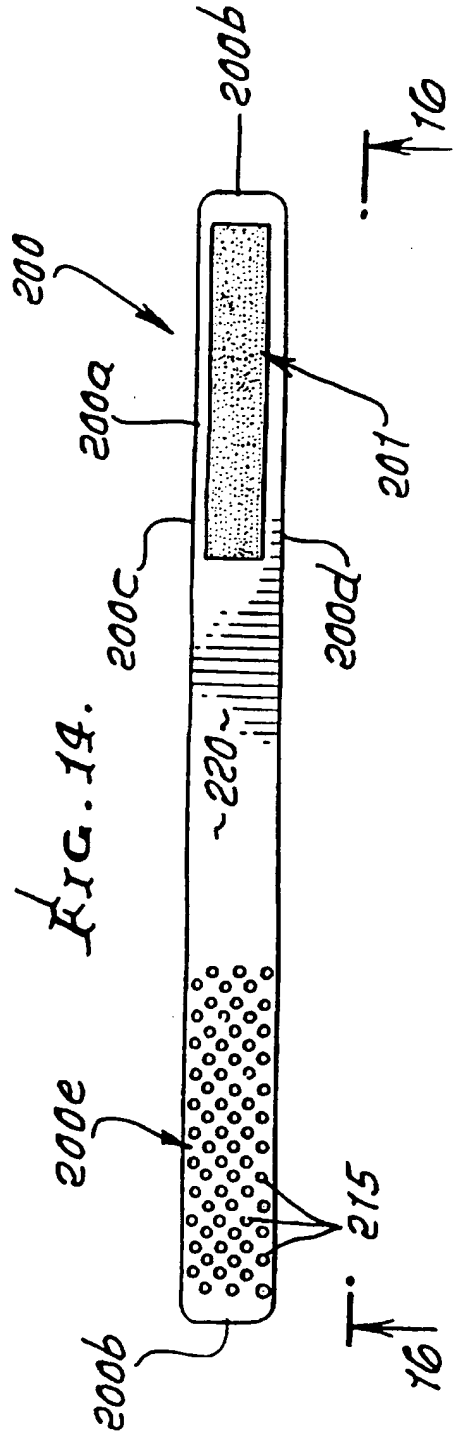

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 17.

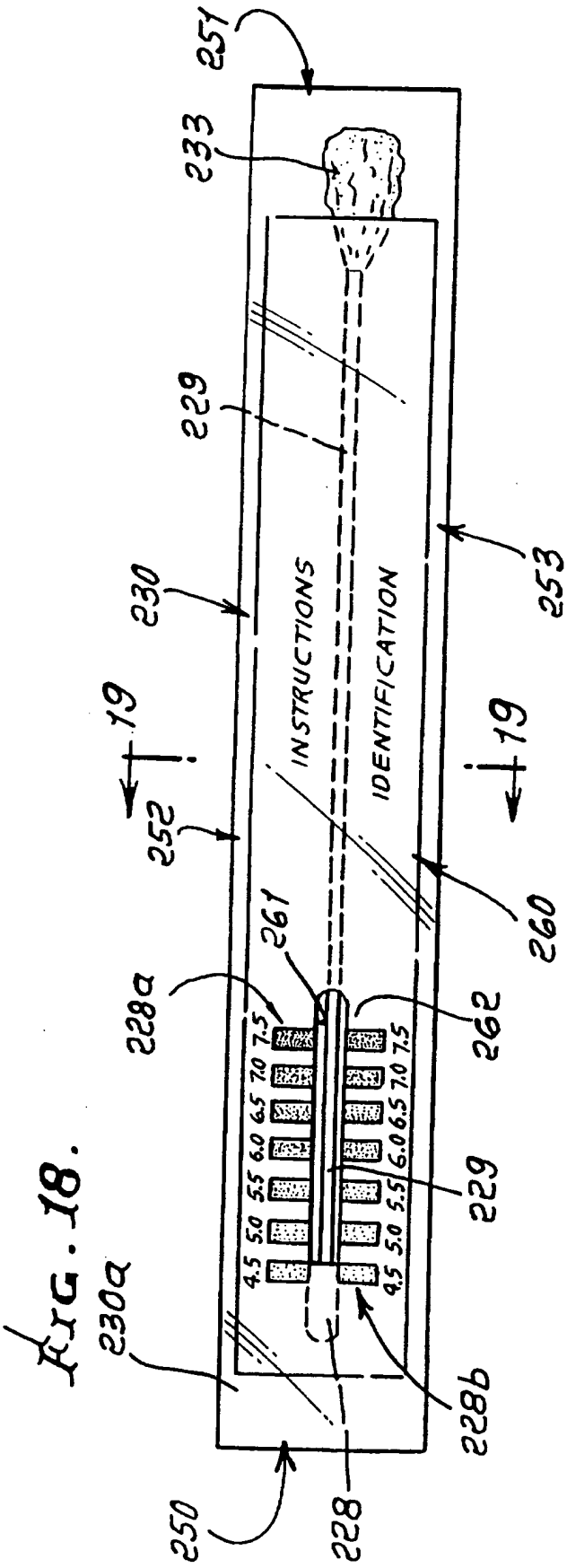
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Fig. 18.

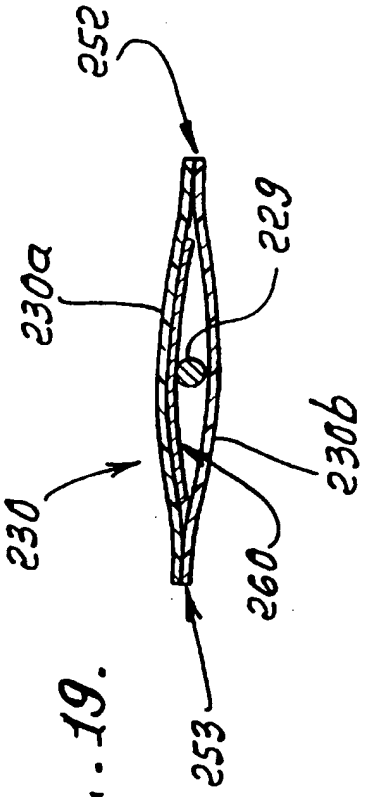
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Fig. 19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14632

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/00
US CL : 600/784

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/562, 572, 573, 584

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2,664,879 A (HARDY) 05 January 1954, Figs. 1-3.	20 --- 1-10, 15, 16, 21-25
Y	US 3,509,872 A (TRUHAN) 05 May 1970, Figs. 1-4.	16, 21-25
Y	US 2,945,491 A (GIBBS) 19 July 1960, Figs. 1-4.	22
Y	BACHMEN, G., The estradiol vaginal ring -- a study of existing clinical data, Elsevier, Maturitas, Journal of the Climacteric & Postmenopause, 22 Suppl. (1995), pages 519-529.	1-10, 15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 NOVEMBER 1997	Date of mailing of the international search report 05 DEC 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MAX HINDENBURG Telephone No. (703) 308-3130

Form PCT/ISA/210 (second sheet)(July 1992)*